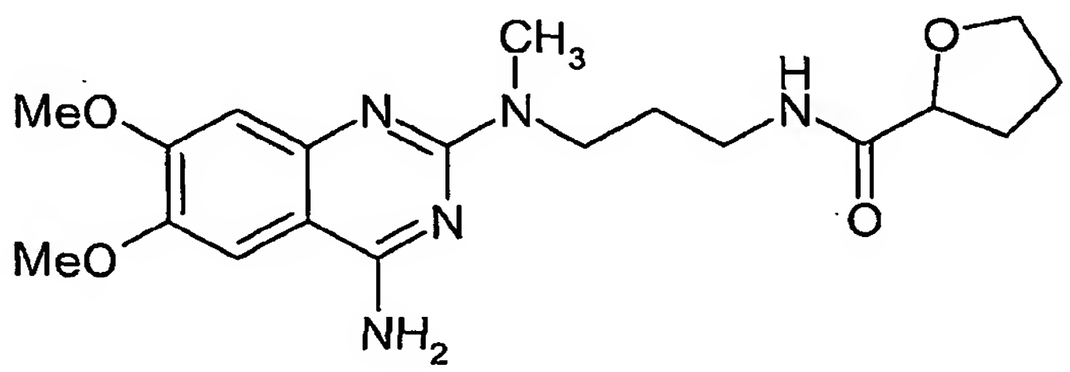
CRYSTALLINE ALFUZOSIN BASE

FIELD OF THE INVENTION

The present invention relates to crystalline solid of-alfuzosin base and processes for preparation of the said crystalline solid of alfuzosin base.

BACKGROUND OF THE INVENTION

U.S. Patent No. 4,315,007 disclosed 4-amino-6,7-dimethoxyquinazol-2-yl alkylenediamine derivatives. The compounds are antihypertensive agents. Among them alfuzosin, chemically N-[3-[(4-amino-6,7-dimethoxy-2-quinazolinyl)methylamino]propyl]tetrahydro-2-furancarboxamide is the most important antihypertensive agent. Alfuzosin is represented by the following structure:



Processes for the preparations of alfuzosin hydrochloride and related compounds were described in U.S. Patent No. 4,315,007 and GB Patent No. 2231571 . U.S. Patent No. 5,545,738 disclosed a dihydrate form of alfuzosin hydrochloride, which is also mentioned about the anhydrous, trihydrate and tetrahydrate forms of alfuzosin hydrochloride. The process for the preparation of crystalline solid of alfuzosin base is not disclosed in the prior art. We have discovered that alfuzosin base can be obtained in crystalline solid. Since the crystalline alfuzosin is obtained with high purity, the said crystalline solid can be used to obtain pharmaceutically acceptable salts of alfuzosin in high purity. It has been found that purification of impure alfuzosin base is practically advantageous when compared with the purification of a salt of it.

One object of the present invention is to provide crystalline solid of alfuzosin base.

Another object of the present invention is to provide processes for preparing crystalline alfuzosin base.

Another object of the present invention is to provide purification methods to obtain high purity alfuzosin base and pharmaceutically acceptable salts via crystalline alfuzosin base.

DETAILED DESCRIPTION OF THE INVENTION

According to one aspect of the present invention, there is provided a process for preparation of crystalline solid of alfuzosin base, the said process comprises stirring a suspension of impure or noncrystalline alfuzosin base in a ketonic solvent or an alcoholic solvent or mixture thereof. The crystalline alfuzosin base may be collected by filtration or centrifugation.

Preferable ketonic solvent is selected from acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl isopropyl ketone and methyl tert-butyl ketone; most preferable ketonic solvents are acetone and methyl isobutyl ketone; preferable alcoholic solvent is selected from methanol, ethanol, isopropyl alcohol and tert-butyl alcohol; and most preferable alcoholic solvents are methanol and ethanol.

Preferably the suspension is stirred for at least 30 minutes at below boiling temperature of the solvent used, more preferably for 1 hour to 4 hours at 25 - 60^{0}C.

According to another aspect of the present invention, there is provided a process for preparation of crystalline solid of alfuzosin base, the said process comprises dissolving alfuzosin base in a ketonic solvent or an alcoholic solvent or mixture thereof and crystallizing alfuzosin base from the solution. The crystalline alfuzosin base may be collected by filtration or centrifugation.

Crystallization may be initiated by a method usually known in the art such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution or a combination thereof.

Preferable ketonic solvent is selected from acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl isopropyl ketone and methyl tert-butyl ketone; most preferable ketonic solvents are acetone and methyl isobutyl ketone; preferable alcoholic solvent is selected from methanol, ethanol, isopropyl alcohol

and tert-butyl alcohol; and most preferable alcoholic solvents are methanol and ethanol.

According to another aspect of the present invention, there is provided a process for preparation of crystalline solid of alfuzosin base, the said process comprises treating an acid addition salt of alfuzosin with a base to liberate alfuzosin base, isolating by forcible or spontaneous crystallization from a ketonic or alcoholic solvent. The crystalline alfuzosin base may be collected by filtration or centrifugation.

Spontaneous crystallization refers to crystallization without the help of an external aid such as seeding, cooling etc., and forcible crystallization refers to crystallization with the help of an external aid.

Forcible crystallization may be initiated by a method usually known in the art such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution or a combination thereof.

The treatment of the acid addition salt with base is carried out in any solvent and the selection of solvent is not critical. A wide variety of solvents such as chlorinated solvents, hydrocarbon solvents, ether solvents etc., may be used.

The base can be inorganic or organic. Preferable base is an inorganic base selected from alkali metal hydroxides, carbonates and bicarbonates. Preferable alkali metal is sodium or potassium.

Preferable ketonic solvent is selected from acetone, methyl ethyl ketone, methyl isobutyl ketone, methyl isopropyl ketone and methyl tert-butyl ketone; most preferable ketonic solvents are acetone and methyl isobutyl ketone; preferable alcoholic solvent is selected from methanol, ethanol, isopropyl alcohol and tert-butyl alcohol; and most preferable alcoholic solvents are methanol and ethanol.

Alfuzosin or a salt thereof used as starting material in the present invention can be prepared by known methods (for example U.S. Patent No. 4,315,007) by reacting N_1-(4-Amino-6,7-dimethoxyquinazol-2-yl)-N_1-methyl propylenediamine with activated tetrahydro-2-furoic acid and optionally converting into the said salt. It has been found that when activated tetrahydro-2-furoic acid is added to N_1-(4-Amino-6,7-dimethoxyquinazol-2-yl)-N_1-methylpropylenediamine, the diamine compound is reacted to a greater extent to form alfuzosin than when the diamine compound is added to activated

tetrahydro-2-furoic acid. Therefore, it is advantageous to prepare alfuzosin, which constitutes another aspect of the present invention, by adding activated tetrahydro-2-furoic acid to diamine compound rather than by adding diamine compound to activated tetrahydro-2-furoic acid.

Activated tetrahydro-2-furoic acid refers to tetrahydro-2-furoic acid having its carboxylic acid group in a conventional activated form.

Isolation of alfuzosin base as crystalline solid affords pure alfuzosin, which can be converted into pharmaceutically acceptable salts of alfuzosin. The isolation avoids multiple purification steps of the pharmaceutically acceptable salts of alfuzosin.

In a preferred process, pharmaceutically acceptable salts of alfuzosin such as alfuzosin hydrochloride in pure form can be obtained directly by isolating alfuzosin base as impure product from the reaction mixture, isolating the base as crystalline solid, converting into the salt and isolating the salt formed.

In another preferred process, impure or noncrystalline alfuzosin base is suspended in a ketonic or an alcoholic solvent, stirred for atleast 30 minutes at about 25 - 60^{0}C, filtered or centhfuged, the obtained solid is dissolved in an alcoholic or ketonic solvent and crystallized and filtered to give alfuzosin base as crystalline solid.

In another preferred process, an acid addition salt of alfuzosin in impure form is dissolved in an alcoholic or ketonic solvent, a base is added to liberate alfuzosin base and alfuzosin base is isolated as a crystalline solid.

'Impure' in the specification refers to having HPLC purity 95% or less than 95% and 'pure' refers to having HPLC purity more than 95%.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a Differential Scanning Calorimetry of crystalline solid of alfuzosin base.

Figure 2 is an Infra-red spectrum of crystalline solid of alfuzosin base.

Figure 3 is a x-ray powder diffraction spectrum of crystalline solid of alfuzosin base.

DSC (Differential Scanning Calorimetry) measurements were performed with a DSC Q10 (TA Instruments, Inc.). About 3 mg of the powder was placed in

an open aluminum pan and it is crimped with an aluminum lid. The crimped sample is then placed in the DSC cell opposite to empty aluminum pan(as reference) and the sample was scanned at 10°C/min from 50°C to 280°C. A typical DSC thermogram of crystalline solid of alfuzosin base is shown in figure 1.

FT-IR spectroscopy was carried out. with a Perkin-Elmer spectrum GX spectrometer. For the production of the KBr compacts approximately 2 mg of sample was powdered with 200 mg of KBr. The spectra were recorded in transmission mode ranging from 4000 to 400 cm^{-1}. A typical infra-red spectrum of crystalline solid of alfuzosin base is shown in figure 2.

x-Ray powder diffraction spectrum was measured on a Bruker axs D8 advance x-ray powder diffractometer having a Copper-K α radiation. Approximately 500 mg of sample was gently flattened on a sample holder and scanned from 2 to 50 degrees two-theta, at 0.03 degrees two-theta per step and a step time of 0.5 seconds. The sample was simply placed on the sample holder. The sample was rotated at 30 rpm at a voltage 40 KV and current 35 mA. A typical x-ray powder diffraction spectrum of crystalline solid of alfuzosin base is shown in Figure 3.

The invention will now be further described by the following examples, which are illustrative rather than limiting.

Comparative example

Step-I:

N_1-(4-Amino-6,7-dimethoxyquinazol-2-yl)-N_1-methylpropylenediamine hydrochloride (75 gm) is added to a mixture of methylene dichloride (500 ml) and triethylamine (25 gm) and stirred for 1 hour at 25 - 30°C. Then the reaction mass is added to a mixture of tetrahydro-2-furoic acid (54 gm), methylene dichloride (375 ml) and carbonyl diimidazole (75 gm) at 40 - 45°C and stirred for 3 hours at the same temperature. The reaction mass is then cooled to 20 - 25°C and the mass is filtered over hi-flo. To the filtrate is added water (500 ml) under stirring, the pH is adjusted to 12 using 10% NaOH solution, and washed twice with water. Then the organic layer is collected, washed with water (1000 ml) and then washed with NaCl solution (500 ml). The resulting organic layer is dried

over sodium sulphate and distilled under vacuum to give oily residue (HPLC purity: 78.80%).

Step-II:

The residue obtained in step-I is added to isopropyl alcohol (850 ml), cooled to 20^{0}C and dry HCl gas is passed under stirring till the pH is reduced to 2. Then the resulting white solid is stirred for 1 hour at 25 - 30^{0}C, the solid is filtered under N_2 atmosphere, washed with isopropyl alcohol (50 ml) and dried at 50^{0}C for 3 hours to give 70 gm of alfuzosin hydrochloride (HPLC purity: 91%).

Example 1

Step-I :

Alfuzosin hydrochloride (70 gm, obtained in step-II of comparative example, HPLC purity: 91%) is added to a mixture of methylene dichloride (700 ml) and water (350 ml), and the pH is adjusted to 12 with 10% NaOH solution at 20 - 25^{0}C. The contents are stirred for 15 minutes and the layers are separated. Then the aqueous layer is collected and re-extracted using methylene dichloride (350 ml). The organic layers are combined, washed with water (1000 mi) and then washed with 10% NaCl solution (500 ml). Then the organic layer is dried over sodium sulphate and distilled off the solvent under vacuum. Acetone (300 ml) is added and stirred for 1 hour 30 minutes at 40 - 45^{0}C. Then the contents are cooled to 25 - 30^{0}C and stirred for 2 hours. The solid is filtered, washed with acetone (50 ml) and then with diisopropyl ether (50 ml) under N_2 atmosphere, and dried at 50 - 55^{0}C for 4 hours to give 60 gm of alfuzosin base (HPLC purity: 97%).

Step-II :

The above alfuzosin base is suspended in acetone (300 ml), the suspension is stirred for 1 hour at 40 - 45^{0}C and cooled to 20 - 25^{0}C. Then the solid is filtered, washed with acetone (50 ml) and then with diisopropyl ether (50 ml), and dried at 50 - 55^{0}C for 4 hours to give 50 gm of alfuzosin base (HPLC purity: 99.3%).

Step-III :

The above alfuzosin base is added to acetone (500 ml), dry HCl gas is passed till the pH is reduced to 2 and stirred for 1 hour under N_2 atmosphere. Then the reaction mass is filtered under N_2 atmosphere, washed with acetone

(50 ml) and dried at 55 - 60^{0}C for 4 hours to give 37.5 gm of 99.3 % pure alfuzosin hydrochloride.

Example 2

Step-I:

Tetrahydro-2-furoic acid (54 gm) is dissolved in methylene dichloride (375 ml) at 25 - 30^{0}C, cooled to 5 - 10^{0}C and carbonyl diimidazole (75 gm) is added to the solution. The contents are stirred for 10 minutes, the temperature is raised to 40 - 45^{0}C and maintained for 1 hour at the same temperature. Then the reaction mass is added to a mixture of Nr(4-Amino-6,7-dimethoxyquinazol-2-yl)-Ni-methylpropylenediamine hydrochloride (75 gm), methylene dichloride (500 ml) and triethylamine (25 gm) at 40 - 45^{0}C and maintained at the same temperature for 3 hours. The reaction mass is cooled to 20 - 25^{0}C and the mass is filtered over hi-flo. To the filtrate is added water (500 ml) under stirring, the pH is adjusted to 12 using 10% NaOH solution, and washed twice with water. Then the organic layer is collected, washed with water (1000 ml) and then washed with NaCl solution (500 ml). The resulting organic layer is dried over sodium sulphate and distilled under vacuum to give oily residue (HPLC Purity: 79.8%).

Step-II:

The above residue is suspended in acetone (300 ml), stirred for 30 minutes at 40 - 50^{0}C and cooled to 25 - 30^{0}C. Then the reaction mass is stirred for 4 hours at 25 - 30^{0}C, the solid obtained is filtered, washed with acetone (50 ml) and dried for 4 hours at 50 - 55^{0}C to give 60 gm of alfuzosin base (HPLC purity: 97%).

Step-III:

The above alfuzosin base is added to acetone (300 ml) and stirred for 30 minutes at 50 - 55^{0}C. The contents are cooled to 25 - 30^{0}C and stirred for 2 hours. Then the solid obtained is filtered, washed with acetone (50 ml) and dried at 50 - 55^{0}C for 4 hours to give 40 gm of alfuzosin base (HPLC purity: 99.56%). The Differential Scanning Calorimetry (DSC), Infra-red (IR) and x-Ray Powder diffraction spectrums of alfuzosin base is essentially same as those shown in Figures 1, 2 and 3 respectively.

Step-IV:

Alfuzosin base obtained above is added to acetone (400 ml), dry HCi gas is passed till the pH of the reaction mass reaches 2 under N_2 atmosphere and stirred for 1 hour at 20 - 25^{0}C. Then the reaction mass is filtered under N_2 atmosphere, washed with acetone (40 ml) and dried at 65 -70^{0}C for 10 hours to give 40 gm of 99.5 % pure alfuzosin hydrochloride.

Example 3

Oily residue (2.0 gm, HPLC purity: 79.8 %, obtained as in step-I of example 2) is added to methyl isobutyl ketone (100 ml) and heated to 80 - 85^{0}C to form a clear solution. The solution is cooled to 25 - 30^{0}C and stirred for 1 hour at the same temperature. Then the solution is cooled to 0 - 5^{0}C and stirred for 1 hour at 0 - 5^{0}C. Then the resulting solid is filtered and dried to give 1.0 gm of the 99.69% pure alfuzosin base. The Differential Scanning Calorimetry (DSC), Infra-red (IR) and x-Ray Powder diffraction spectrums of alfuzosin base is essentially same as those shown in Figures 1, 2 and 3 respectively.

Example 4

Alfuzosin base (5 gm, HPLC purity: 97%, obtained as in step-II of example 2) is added to acetone (250 ml), heated to 55 - 60^{0}C and stirred for 15 minutes at the same temperature to form a clear solution. The solution is filtered, removed the undissolved solids and the filtrate is stirred for 12 hours at 25 - 30^{0}C. The reaction mass is cooled to 10 - 15^{0}C and stirred for 2 hours at 10 - 15^{0}C. Then the resulting solid is filtered and dried at 50 - 60^{0}C for 4 hours to give 3 gm of 99.77% pure alfuzosin base. The Differential Scanning Calorimetry (DSC), Infra-red (IR) and x-Ray Powder diffraction spectrums of alfuzosin base obtained is shown in Figures 1, 2 and 3 respectively.

Example 5

Alfuzosin base (5 gm, HPLC purity: 97%, obtained as in step-I of example 1) is added to methanol (55 ml) and heated to reflux to form a clear solution. The solution is cooled to 25 - 30^{0}C and stirred for 12 hours at the same temperature. Then the solution is cooled to 10 - 15^{0}C and stirred for 2 hours. The resulting solid is filtered, washed with methanol (5 ml) and dried at 50 - 60^{0}C for 4 hours to give 3.5 gm of 99.95% pure alfuzosin base. The Differential

Scanning Calorimetry (DSC), Infra-red (IR) and x-Ray Powder diffraction spectrums of alfuzosin base is essentially same as those shown in Figures 1, 2 arid 3 respectively.